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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/256,156	02/24/1999	STEPHEN GILLIES	LEX-003	9492

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/256,156	GILLIES ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-8,10,27,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-8,10,27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05 May 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 14, 2004 has been entered into the record and has been fully considered. Claims 2, 5, 9, 11-26, and 28 have been canceled. Claims 1, 3, 4, 6-8, 10, and 27 are amended. Claims 29 and 30 are new. Claims 1, 3, 4, 6-8, 10, 27, and 29-30 are pending and under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on May 5, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

The objection to the specification for failure to comply with the sequence disclosure requirements is withdrawn in view of the amendments made to the specification and Figure 6.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 6-8, 10, 29, and 30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a "region" of a gene construct. As stated above in 35 U.S.C. 101, a patent may be granted for a process, machine, article of manufacture, or composition of matter. Claims 1, 3, 6-8, 10, 29, and 30 are portions of a composition. The rejections may be obviated by deleting the word "region" from the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 7 and 8 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendments made to claims 7 and 8.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is drawn to an antibody-based fusion protein comprising a portion of a heavy chain comprising "at least a portion of an IgG3 constant region having a mutation or a deletion at one or more amino acids selected from the group consisting of Leu_{281}, Leu_{282}, Gly_{283}, Gly_{284}, Asn_{344}, and Pro_{378}". As the claim is written, it is not clear whether the antibody-based fusion protein must have one of the mentioned mutations or deletions because the portion of the IgG3 constant region may or may not contain residues 282-284, 344 or 378. This rejection could be obviated by having the claim drawn to an antibody-based fusion protein comprising a portion of a heavy chain comprising "at least a portion of an IgG3 constant region, wherein the portion of an IgG3 constant region comprises a mutation or a deletion at one or more amino acids selected from the group consisting of Leu_{281}, Leu_{282}, Gly_{283}, Gly_{284}, Asn_{344}, and Pro_{378}."

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3, 6-8, and 10 under 35 U.S.C. 102(a) is withdrawn in view of the Declaration of Stephen Gillies and Kin-Ming Lo.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 6-8, 10, 27, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray *et al.* (U.S. Patent No. 6,444,792) in view of Harvill *et al.* (1995, *Immunotechnology* 1(2): 95-105, submitted in October 7, 1999 IDS and cited in paper no. 26). Claims 1, 29, and 30 are drawn to an antibody-based fusion proteins comprising a portion of an IgG1 or IgG3 CH2 domain with a mutation resulting in reduced binding affinity for an Fc receptor fused at its 3' end to a non-immunoglobulin protein. Claim 3 is drawn to an antibody-based fusion protein comprising a mutation at residue 234, 235, 236, 237 or 297 that results in decreased binding affinity for Fc receptors. Claim 6 is drawn to an antibody-based fusion protein comprising a mutation in a CH2 domain resulting in decreased binding affinity for FcγRI, FcγRII or FcγRIII. Claims 7-10 are drawn to an antibody-based fusion protein wherein the non-immunoglobulin protein is a cytokine such as the interleukin IL-2. Claim 27 is drawn to an antibody-based fusion protein comprising a portion of an IgG4 CH2 domain fused at its C-terminus to the N-terminus of a non-Ig protein.

Gray *et al.* teach antibody-based fusion proteins comprising a modified constant region and a second non-immunoglobulin protein (column 3). The immunoglobulin constant region may comprise a hinge region, a CH2 domain, and a CH3 domain from IgG1, IgG2, IgG3 or IgG4 (column 4, lines 15-17). Gray *et al.* teach the CH2 domain may be modified to reduce interactions with Fc receptors such as FcRI by modifying at least one residue at positions 234, 235, 236 or 237 by substitution, deletion or addition of amino acids (column 9, lines 60-64 and column 4, lines 24-33). However, Gray *et al.* do not teach an antibody-based fusion protein wherein the non-immunoglobulin protein is fused at its N-terminus to the C-terminus of the

immunoglobulin segment. Also, Gray *et al.* do not teach an antibody-based fusion protein comprising a cytokine.

Harvill *et al.* teach a fusion protein wherein the N-terminus of a non-IgG protein is fused to the C-terminus of IgG3. More specifically, Harvill *et al.* teach an IgG3-IL-2 fusion protein. It would have been obvious to a person of ordinary skill in the art to combine the teachings of Harvill *et al.* and Gray *et al.* in order to generate antibody-based fusion proteins comprising IL-2 wherein the antibody-based fusion protein has reduced binding affinity for Fc receptors and an increased serum half-life. One of ordinary skill in the art would have been motivated to do so because Gray *et al.* teach antibody-based fusion proteins having an increased serum half-life, and Harvill *et al.* teach the therapeutic value of IL-2 is limited by its short half-life. Thus, a person of ordinary skill in the art would have expected to be able to generate antibody-based fusion proteins having an increased half-life wherein the immunoglobulin part is fused to the N-terminus of IL-2.

Claim 3 is further rejected under 35 U.S.C. 103(a) as being unpatentable over Gray *et al.* (U.S. Patent No. 6,444,792) in view of Winter *et al.* (U.S. Patent No. 5,624,821 cited in paper no. 26). Claim 3 is as stated above. Gray *et al.* teach mutations at positions 234, 235, 236 and/or 237 may reduce interactions with Fc receptors, however Gray *et al.* do not teach any benefits of mutations at residue 297. Winter *et al.* teach that mutating residues 234, 235, 236 and/or 297 alters an effector function of an immunoglobulin as compared with an unmodified form (see column 5, lines 42-58; column 7, lines 21-28, and claim 1). It would have been obvious to a person of ordinary skill in the art to make an antibody-based fusion protein wherein the CH2 domain has a mutation occurring at residue 297 that results in reduced binding affinity for an Fc receptor. One of ordinary skill in the art would have been motivated to do so because Gray *et al.* teach the benefits of engineering antibody-based fusion proteins with reduced affinity for Fc receptors. Moreover, a person of ordinary skill in the art would have expected success in engineering the modified antibody-based fusion protein.

Conclusion

NO CLAIMS ARE ALLOWED.

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

International Publication No. WO 96/18412 (Strom *et al.*)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RBK
3/29/04

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER